BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5] :		(11) International Publication Number:	WO 92/09299
A61K 37/02, 47/34	A1	(43) International Publication Date:	11 June 1992 (11.06.92)

(21) International Application Number: PCT/HU91/00050

(22) International Filing Date: 27 November 1991 (27.11.91)

(30) Priority data:
7653/90 27 November 1990 (27.11.90) HU

(71) Applicant *(for all designated States except US)*: BIOGAL GYÓGYSZERGYÁR RT. [HU/HU]; Pallagi u. 13, H-4042 Debrecen (HU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : ORBÁN, Ernő [HU/HU]; Ménesi út 31/A, H-1118 Budapest (HU). TOMORI, Lászlóné [HU/HU]; Berda J. u. 42, H-1045 Budapest (HU). KÜRTHY, Mária [HU/HU]; Bessenyei u. 24/B, H-1139 Budapest (HU). BALOGH, Tibor [HU/HU]; Róbert K. Krt. 12/c, H-1138 Budapest (HU). JASZLITS, László [HU/HU]; Maros u. 4, H-1129 Budapest (HU). MORAVCSIK, Imre [HU/HU]; Mester u. 38, H-1095 Budapest (HU). KOVÁCS, István [HU/HU]; Bekecs u. 11/b, H-4028 Debrecen (HU). JUSZTIN, Istvánné [HU/HU]; Nagyerdei krt. 30, H-4028 Debrecen (HU). JÁNCSÓ, Sándor [HU/HU]; Kardos u. 28, H-4028 Debrecen (HU). TAKÁCS, Erzsébet [HU/HU]; Böszörményi út 119, H-4023 Debrecen (HU). KISS, Tamásné [HU/HU]; Bem tér 11/c, H-4026 Debrecen (HU). KOVÁCS, Antalné [HU/HU]; Lefkovics V. u. 72, H-4028 Debrecen (HU).

(74) Agent: DANUBIA; Bajcsy Zs. u. 16, H-1368 Budapest V. (HU).

(81) Designated States: AT (European patent), AU, BE (European patent), BG, CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, RO, SE (European patent), SU+,US.

Published
With international search report.

(54) Title: ORAL PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN AND PROCESS FOR PREPARING SAME

(57) Abstract

The invention relates to therapeutically usable novel oral solutions, containing cyclosporin as active ingredient, which possess advantageous absorption characteristics. The invention also relates to a process for preparing these solutions. The solutions according to the invention comprise 1 part by mass of one or more cyclosporin(s) dissolved in a mixture containing 4 to 50 parts by volume of propylene glycol, 0 to 25 parts by volume of ethanol and 0.01 to 5 parts by mass of a polyoxyethylene/polyoxypropylene block polymer in homogenized state. Based on examinations carried out at 100 °C, the stability of solutions prepared according to the invention does not differ from that of the commercially available Sandimmun oral solution.

+ See back of page

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU+	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

ORAL PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN AND PROCESS FOR PREPARING SAME

This invention relates to therapeutically useable novel cyclosporin-containing solutions possessing advantageous absorption characteristics and suitable for oral administration. Furthermore, the invention relates to a process for preparing these solutions.

Cyclosporins are cyclic oligopeptides of microbiological origin. Due to its immunosuppressive effect, cyclosporin is widely used: in kidney, liver, heart, lung, pancreas, skin and cornea transplatations in order to prevent the ejection of the transplanted organ; in bone marrow transplantations, to inhibit the antibody production of the transplanted bone marrow against the host organism (graft-versus-host disease); further for healing autoimmune diseases such as rheumatoid arthritis, diabetes mellitus I, systematic lupus erythematosis, scleroderma, Wegener's granulomatosis, eosinophilic fascitis, primary liver cyrrhosis, Graves' and Crohn's diseases. Similarly, it is used for the treatment of myasthenia gravis, multiplex sclerosis and psoriasis.

Cyclosporins are practically water-insoluble substances formed from neutral amino acids of hydrophobic character. As a consequence of their high molecular weight (over 1000), poor water-solubility and weak absorption [O. Siddiqui and

Y.W. Chien: Nonparenteral Administration of Peptide and Protein Drugs. CRC Crit. Rev. Ther. Drug Car. 3, 195-208 (1986)], they are absorbed only to an insignificant extent from the gastrointestinal tract when administered directly or in the traditional pharmaceutical formulations (tablets, capsules and the like).

Thus, the most important aim of developing cyclosporin-containing pharmaceutical compositions is to find a solution for this problem, by means of which the absorption and bioavailability of the active agent can successfully be improved.

A number of methods are known from the literature, by the use of which the absorption and bioavailability of cyclosporin active agents can be increased. From these, the methods worked out for preparing solutions for oral administration are briefly summarized hereinafter.

1. Dissolution of cyclosporin in sesame oil and/or in the mixture of non-ionic surfactants and/or transesterified nonionic triglycerids and/or lecithins, ethyl oleate and transesterified nonionic surfactants and/or in a neutral oil (see e.g. the Swiss patent specification No. 636,013).

2. Dissolution of cyclosporin in the mixture of a transesterified product of a native vegetable oil with a polyalkylene polyol (such as Labrafil M 1944 CS) as well as a vegetable oil and ethanol (see e.g. the Swiss patent specification No. 641,356 and the United States patent specification No. 4,388,307).

The above method 1 is suitable for preparing a drink solution or drink emulsion whereas method 2 is useful for the preparation of a water-dispersible oral solution. It should be noted that the commercially available oral Sandimmun ^{R} solution (Sandoz Ltd., Basel, Switzerland) is prepared according to method 2.

Compositions with relatively high active-ingredient content can be prepared by using both methods. The disadvantage of these compositions lies in that vegetable oils are used as carrier additives which, on the one hand, endow the compositions with an unpleasant oily taste and, on the other hand, these compositions become rancid during a longer storage whereby a further undesired alteration may occur in the taste and odour of the compositions. Although the degr of rancidification could be limited by antioxidants, this process cannot completely be eliminated. Thus, the oral compositions prepared according to the above methods can be commercialized with only a relatively short expiration time.

The aim of the present invention is to provide therapeutically useful, oral cyclosporin-containing solutions which are free from the drawbacks of the known solutions, contain the cyclosporin active ingredient(s) - in opposition to the known solutions - dissolved in a both chemically and microbiologically stable hydrophilic and not hydrophobic medium and provide advantageous absorption f th active ingr dient(s) from the gastrointestinal tract after dilution with water or aque us s lutions.

During our investigations it has surprisingly been ob-

served that the above aim could completely be achieved by using suitable hydrophilic pharmaceutical additives (solvents and surface-active agents). It has been stated that the dissolution of one or more cyclosporin(s) in the mixture of propylene glycol and a polyoxyethylene/polyoxypropylene block polymer, optionally in the presence of ethanol, results in solutions from which, after mixing with water or aqueous solutions (e.g. fruit juices, milk, chocolate-drinks), the cyclosporins precipitate in the form of finely distributed, dispersed particles. The cyclosporins are rapidly absorbed from the gastrointestinal tract due to the large surface of particles of the active ingredient as well as under the effect of the block polymer.

The above recognition is also therefore surprising since it is known that the gastrointestinal absorption of drugs of hydrophobic character like the cyclosporins (e.g. griseofulvin, chlorothiazide, nitrofurantoin, indoxol and the like) proceeds with a substantially better efficiency from oily solutions or oil-in-water emulsions than from the corresponding aqueous suspensions of fine distribution. In opposition to the use in empty stomach, the blood levels of these drugs are strongly enhanced by consuming fat-rich foods (e.g. butter, cream) before the administration [M. Gibaldi: Biopharmaceutics and Clinical Pharmaceutics, Lea and Febiger, Philadelphia (1984)].

It is supported by the above-mentioned facts that the absorption of substances of hydrophobic character can preferably be improved by preparing and using lipid-type matric s

or solutions. At the same time it is surprising that the absorption of cyclosporins from hydrophilic systems to the same extent as above can be ensured while eliminating lipid-like substances.

The animal experiments carried out for proving our above statements are discussed hereinafter.

Solution to be tested: a solution containing cyclosporin A, prepared according to Example 2, in a concentration of 100 mg/ml.

Test method: 6 male New Zealand rabbits with 2.7 to 3.5 kg of body weight were used in the animal tests. The animals were kept separately at 20±2 °C and received standard rabbit food (LATI, Gödöllő) as well as tap water ad libitum. (No food was given starting from the afternoon of the day before administration.) The solution to be tested was administered in a dose of 25 ml/kg of body weight through a probe and washed in by the same volume of tap water.

Five ml of blood each were taken from the ear vein of the rabbits before administration and then 1, 2, 3, 4, 6, 12 and 24 hours after administration.

The concentration of cyclosporin A in the blood samples was determined by HPLC method. The results obtained are shown in Figure 1 wherein blood-level values are plotted against time elapsed after oral administration.

It can be stated from the data that cyclosporin A was well adsorb d from the orally administered solution. The highest blood l v l d v lop d 2 hours following administration. Only an extrem ly low amount f cyclosp rin could b

detected in the blood after 24 hours.

Based on the above results, the invention relates to a novel, therapeutically usable oral solution containing cyclosporin as active ingredient in admixture with hydrophilic solvents and surface-active agents, which comprises 1 part by mass of one or more cyclosporin(s) dissolved in a mixture containing 4 to 50 parts by volume of propylene glycol, 0 to 25 parts by volume of ethanol and 0.01 to 5 parts by mass of a polyoxyethylene/polyoxypropylene block polymer in homogenized and, if desired, sterile state.

According to an other aspect of the invention, there is provided a process for the preparation of the above novel oral solution, which comprises dissolving 1 part by mass of one or more cyclosporin(s) in a mixture containing 4 to 50 parts by volume of propylene glycol, 0 to 25 parts by volume of ethanol and 0.01 to 5 parts by mass of a polyoxyethylene/-polyoxypropylene block polymer, homogenizing the solution obtained and, if desired, sterilizing it by filtration.

By using the process according to the invention, hydrophobic cyclopropins, which are insoluble or weakly soluble in the common pharmaceutical additives, e.g. cyclosporin A and cyclosporin G, or any of their mixtures of desired ratio can be brought into a solution being hydrophilic in character and subsequently a dispersion with extremely fine particle size can be prepared from this solution.

Synthetic polyoxyethylene/polyoxypropylen block polymers [nomenclature according to CTFA (Cosmetic, Toiletry and

Fragrance Association): Poloxamers] with a molcular mass between 1000 and 15,500, preferably Poloxamer-124, -184, -185, -188, -237, -335, -338 and -407 or their mixtures may be used as surface-active agents in the compositions according to the invention. These block polymers are commercially available under the trade name Pluronic or Lutrol, respectively (manufacturer: BASF Wyandotte Corp. Michigan, USA or BASF, Ludwigshafen, Germany). A great advantage of polyoxyethylene/polyoxypropylene block polymers lies in that they are tasteless, extremely stable and possess significant bactericidal or bacteriostatic effects; therefore, no other additives are needed for the microbiological preservation of solutions prepared by using these block polymers [Pluronic Polyols Toxicity and Irritation Data, 3rd Edition, BASF Wyandotte Corp. Wyandotte, Michigan, USA (1971)].

The ratio of propylene glycol, ethanol and surface-active agents which can be be used in the cyclosporin-containing oral solutions according to the invention is determined in each case by the cyclosporin concentration of the composition to be prepared.

Thus, propylene glycol is preferably used in a volume ratio of (4 to 50):1; ethanol is preferably used in a volume ratio of (0 to 25):1 and the polyoxyethylene/polyoxypropylen block polymer is preferably employed in a weight ratio of (0.01 to 5):1 in relation to the mass of the cyclosporin(s) us d.

According t a pr f rr d emb dim nt of th process f th invention cycl sporin-containing oral soluti ns ar pre-

pared by dissolving 1 part by mass of cyclosporin and 0.01 to 5 parts by mass of polyoxyethylene/polyoxypropylene block polymer in a mixture containing 4 to 50 parts by volume of propylene glycol and 0 to 25 parts by volume of ethanol (or in 4 to 50 parts by volume of propylene glycol when no ethanol is used) at room temperature (about 20 °C).

If desired, the solution obtained is filtered through a regenerated cellulose membrane (Sartorius SM 116 04 with a pore size of 0.8 μm) and filled into suitable glass bottles in the doses required.

The pharmaceutical composition prepared as described above can be administered after dilution with water or aqueous solutions. A suitably dosed (weighed) part of the solution is poured into 100-150 ml of water, fruit juice or cold cocoa drink, mixed and then orally administered.

Thus, by using the process according to the invention, well-absorbable oral cyclosporin compositions can be prepared in a simple way by using additives commonly used in the therapeutical practice. The compositions thus prepared are in themselves tastless, stable and do not require particular storage conditions and can be stored for an unlimited period.

The invention is illustrated in detail by the following non-limiting Examples.

Example 1

Preparation of an oral solution containing cyclosporin A

After dissolving 100 g of cyclosporin A in 490 ml of propyl ne glycol (USP XXII quality) und r stirring at room

temperature (about 20 °C) 5 g of a polyoxyethylene/polyoxypropylene block polymer of a molecular mass of about 2200 [CTFA-name: Poloxamer-124) USNF XVII Suppl. I quality] are mixed to the above solution. After supplementing the volume to 500 ml by adding propylene glycol, the solution is filtered through a regenerated cellulose membrane (Sartorius SM 116 04) under nitrogen gas pressure. The composition thus obtained is filled into glass bottles suitable for storage.

The thus-pepared composition contains 200 mg/ml of cyclosporin A.

Example 2

Preparation of an oral solution containing cyclosporin A

10 g of polyoxyethylene/polyoxypropylene block polymer (with a molecular mass of about 8400 (CTFA-name: Poloxamer-188) USNF XVII Suppl. I quality) are added to a solution prepared by dissolving 100 g of cyclosporin A in 300 ml of ethanol (USP XXII quality) while stirring at room temperature (about 20 °C). The solution is stirred under identical conditions until the additive is dissolved, then it is filled up to a volume of 1000 ml with propylene glycol (USP XXII quality). The solution is homogenized by stirring, then filtered through a Sartorius SM 116 04 membrane filter under nitrogen gas pressure and the composition is filled into glass bottles suitable for storage.

The composition prepared in this way contains 100 mg/ml of cyclosporin A.

Example 3

Preparation of an oral solution containing cyclosporin G

100 g of cyclosporin G are dissolved in a mixture containing 500 ml of ethanol (USP XXII quality), 2900 ml of propylene glycol (USP XXII quality) and 400 ml (400 g) of polyoxyethylene/polyoxypropylene block polymer with a molecular mass of about 2900 (CTFA name: Poloxamer-184) under stirring at room temperature (about 20 °C), then the solution is filled up to a volume of 4000 ml with propylene glycol.

The mixture is homogenized, then the process described in Example 2 is followed.

The composition prepared in this way contains 25 mg/ml of cyclosporin G.

Example 4

Preparation of an oral solution containing cyclosporin A and cyclosporin G

50 g of cyclosporin A and 50 g of cyclosporin G are dissolved in a mixture containing 300 ml of ethanol (USP XXII quality) and 100 ml of propylene glycol (USP XXII quality) while stirring at room temperature (about 20 °C). After adding 10 g of a polyoxyethylene/polyoxypropylene block polymer with a molecular mass of about 7700 (CTFA-name: Poloxamer-237) and 5 g of a polyoxyethylene/polyoxypropylen block polymer with a molecular mass of about 6500 (CTFA-nam : Poloxamer-335) the solution is stirred until dissolution of th additiv s. The mixture is fill d up to a volume of 1000 ml with pr pyl n glycol, homog niz d and then th procedur

described in Example 2 is followed.

The composition prepared as descirbed above contains 50 mg/ml of cyclosporin A and 50 mg/ml of cyclosporin G.

The composition described in Examples 1 to 4 were subjected to stability examinations. The solutions were stored at 25, 45, 60, 75 and 100 °C, respectively, after filling into brown glass bottles of III hydrolytic class.

Simultaneously with the examination of solutions prepared according to the process of the invention, the stability of the commercially available Sandimmun R drink solution (Sandoz Ltd, Basel, Switzerland) containing 100 mg/ml of cyclosporin A was also examined.

The quantitative determination of cyclosporin A was performed by using HPLC method under the following conditions of chromatography:

Pump: LKB Model 2150

Controller: LKB 2152

Detector: LKB Model 2151 with a variable wave-length UV absorbance at 220 nm, 0.64 AB

LKB Model 2140 serieal diode detector

Injector: Rheodyne, Model 7215, 10 µl of loop injection

Column: BST-Si-100 C 8.7 µm, 25 cm x 0.4 cm stainless steel

Thermostat: LK Model 2155, maintaining the column at 50 °C during th analysis

Eluant: ac tonitrile/wat r/methanol/85 % phosphoric acid (900:525:75:0.075)

Flow rate of the eluant: 1 ml/min

Integrator: LKB Model 2220

Recorder: LKB Model 2210, 10 mV

It has been stated by the above examinations that the stability of solutions prepared according to the process of the invention did not differ from the stability of the commercially available composition. This statement is illustrated in Table I by the results of examinations carried out at 100 °C with a solution containing 100 mg/ml of cyclosporin A (signed as CyA in Table I) prepared in Example 2 according to the invention and, on the other hand, with a Sandimmun ^{R} drink solution of the same concentration.

Table I

Comparative stability examination of oral solutions containing cyclosporin A

	Oral solution of Ex. 2.		Sandimmun oral solution	
Thermal load	CyA content (measured in %)	n (%)	CyA content (measured in %)	n (%)
Untreated	96.1 (n_1)	98.9	99.3	99.8
	96.6 (n_2)		100.6	
	96.9 (n_3)		99.5	

Table I (continued)

	97.6		100.6	
100°/1 hour	99.7	98.9	99.3	100.0
	99.4		100.2	
	96.4		97.5	
100°/5 hours	95.4	95.3	96.6	97.3
	94.1		97.8	
	98.0		98.5	
100°/8 hours	95.2	96.7	97.6	98.1
	97.1		98.0	
	97.8		96.0	
100°/24 hours	98.7	96.6	95.8	95.5
	93.3		94.9	

Claims:

1. A therapeutically usable oral solution containing cyclosporin as active ingredient in admixture with hydrophilic solvents and surface-active agents, which comprises 1 part by mass of one or more cyclosporin(s) dissolved in a mixture containing 4 to 50 parts by volume of propylene glycol, 0 to 25 parts by volume of ethanol and 0.01 to 5 parts by mass of a polyoxyethylene/polyoxypropylene block polymer in homogenized and, if desired, sterile state.

2. A composition as claimed in claim 1, which compris s cyclosporin A or cyclosporin G or a mixture thereof as cyclosporin.

3. A composition as claimed in claim 1 or 2, which comprises using a polyoxyethylene/polyoxypropylene block polymer with a molecular mass between 1000 to 15,500.

4. A process for the preparation of a therapeutically usable oral solution containing cyclosporin as active ingredient by using hydrophilic solvents and surface-active agents, which comprises dissolving 1 part by mass of one or more cyclosporin(s) in a mixture containing 4 to 50 parts by volume of propylene glycol, 0 to 25 parts by volume of ethanol and 0.01 to 5 parts by mass of a polyoxyethylene/ polyoxypropylene block polymer, homogenizing the solution obtained and, if desir d, st rilizing it by filtration.

5. A proc ss as claim d in claim 4, which c mpris s using cycl sporin A or cyclosporin G or a mixture there f as cycl sporin.

6. A process as claimed in claim 4 or 5, which comprises using a polyoxyethylene/polyoxypropylene block polymer with a molecular weight between 1000 and 15,500.

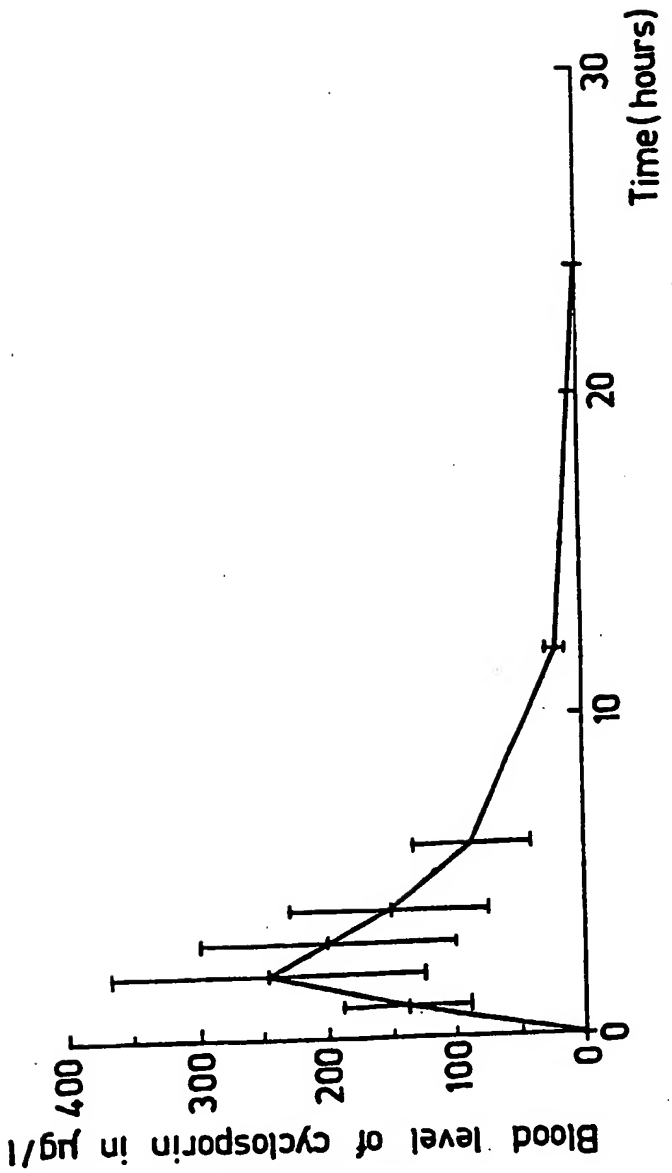
Blood level of cyclosporin in µg/l
400
300
200
100
0
0
10
20
30
Time (hours)

Fig.1

INTERNATIONAL SEARCH REP RT

International Application No PCT/HU 91/00050

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[5]: A 61 K 37/02, 47/34

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
Int. Cl.[5]:	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched 8

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X	GB, A, 2 228 198 (SANDOZ LTD.) 22 August 1990 (22.08.90), see claims.	(1,3)
A	DE, A1, 4 003 844 (SANDOZ-PATENT-GMBH) 16 August 1990 (16.08.90), see the abstract.	(1-3)
A	DE, A1, 3 930 928 (SANDOZ-PATENT-GMBH) 22 March 1990 (22.03.90), see the abstract.	(1)
A	WO, A1, 88/06 438 (THE LIPOSOME COMPANY, INC.), 07 September 1988 (07.09.88), see claims 1 to 4, 7,22 to 25,28.	(1,2,4,5)
A	EP, A1, 0 249 587 (AKTIEBOLAGET HÄSSLE) 16 December 1987 (16.12.87), see page 3, lines 23 to 32.	(1,3)
A	CH, A5, 641 356 (SANDOZ AG) 29 February 1984 (29.02.84), see claims.	(1,2,4,5)
A	US, A, 4 388 307 (CAVANAK) 14 June 1983 (14.06.83), see claims.	(1,2)

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATI N

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04 February 1992 (04.02.92)	12 February 1992 (12.02.92)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif á la demande de brevet international n°

PCT/HU 91/00050

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB-A - 2228198		DE-A1- 4005190	23-08-90
		FR-A1- 2643262	24-08-90
		GB-A0- 8903804	05-04-89
		GB-A0- 9003616	11-04-90
		GB-A1- 2228198	22-08-90
		JP-A2- 2255623	16-10-90
DE-A1- 4003844	16-08-90	AU-A1-49252/90	16-08-90
		BE-AF- 1003009	22-10-91
		CA-AA- 2009533	09-08-90
		DK-A0- 327/90	07-02-90
		DK-A - 327/90	10-08-90
		ES-AF- 2021942	16-11-91
		FI-A0- 900604	07-02-90
		FR-A1- 2642650	10-08-90
		GB-A0- 8903663	05-04-89
		GB-A0- 9002504	04-04-90
		GB-A1- 2230440	24-10-90
		HU-A0- 900701	28-04-90
		HU-A2- 54058	28-01-91
		IL-A0- 93298	29-11-90
		JP-A2- 2235817	18-09-90
		NL-A - 9000299	03-09-90
		NO-A0- 900577	07-02-90
		NO-A - 900577	10-08-90
		SE-A0- 9000441	07-02-90
		SE-A - 9000441	08-08-91
		GB-A0- 8903147	30-03-89
		GB-A0- 8902898	30-03-89
		IL-A0- 93298	29-11-90
		GB-A0- 8902901	30-03-89
		ZA-A - 9000993	30-10-91
		ES-UA- 1012909	01-10-90
DE-A1- 3930928	22-03-90	AU-A1-41400/89	22-03-90
		BE-AF- 1003105	26-11-91
		CH-A - 679118	31-12-91
		DK-A0- 4559/89	15-09-89
		DK-A - 4559/89	17-03-90
		ES-AF- 2020738	16-09-91
		FI-A0- 894342	14-09-89
		FI-A - 894342	17-03-90
		FR-A1- 2636534	23-03-90
		GB-A0- 8902900	30-03-89
		GB-A0- 8920597	25-10-89
		GB-A1- 2222770	21-03-90
		HU-A2- 53541	28-11-90
		IL-A0- 91642	29-04-90
		JP-A2- 2121929	09-05-90
		LU-A - 87586	07-05-91
		NL-A - 8902315	17-04-90
		NO-A0- 893678	14-09-89
		NO-A - 893678	19-03-90
		SE-A0- 8903042	15-09-89
		SE-A - 8903042	11-05-90
		GB-A0- 8902903	30-03-89
		IT-A0- 8948369	15-09-89
		GB-A0- 8821754	19-10-88
		ZA-A - 8907066	29-05-91
		ES-UA- 1011812	16-05-90
		ES-YA- 1011812	16-12-90

WO-A1- 8806438	07-09-88	AU-A1-14818/88	26-09-88
		AU-A1-85985/91	12-12-91
		EP-A1- 355095	28-02-90
		EP-A4- 355095	05-09-90
		JP-T2- 2502719	30-08-90
EP-A1- 249587	16-12-87	AU-A1-70043/87	15-10-87
		AU-B2- 602677	25-10-90
		CN-A -87102758	21-10-87
		CS-A2- 8702587	14-11-89
		CS-B2- 270560	12-07-90
		DD-A5- 263231	28-12-88
		DK-A0- 1549/87	26-03-87
		DK-A - 1549/87	12-10-87
		FI-A0- 871585	10-04-87
		FI-A - 871585	12-10-87
		HU-A2- 43786	28-12-87
		JP-A2-62242613	23-10-87
		NO-A0- 871199	23-03-87
		NO-A - 871199	12-10-87
		NZ-A - 219633	28-11-89
		PH-A - 22494	12-09-88
		PL-A1- 265078	21-07-88
		PT-A - 84663	01-05-87
		PT-B - 84663	16-05-89
		SE-A0- 8601624	11-04-86
		US-A - 4803081	07-02-89
		ZA-A - 8701911	30-12-87
CH-A5- 641356		CH-A - 641356	29-02-84
US-A - 4388307	14-06-83	AR-A1- 223667	15-09-81
		AT-A - 1637/79	15-02-84
		AT-B - 375828	10-09-84
		AU-A1-44862/79	13-09-79
		AU-B2- 528714	12-05-83
		BE-A1- 874628	05-09-79
		CA-A1- 1139667	18-01-83
		CY-A - 1285	05-07-85
		DD- C- 142149	11-06-80
		DE-A1- 2907460	13-09-79
		DE-C2- 2907460	27-09-90
		DK-A - 860/79	08-09-79
		DK-B - 154539	28-11-88
		DK-C - 154539	16-05-89
		ES-A1- 478295	16-05-79
		ES-A5- 478295	15-06-79
		FI-A - 790640	08-09-79
		FI-B - 65914	30-04-84
		FI-C - 65914	10-08-84
		FR-A1- 2419072	05-10-79
		FR-B1- 2419072	22-04-83
		GB-A1- 2015339	12-09-79
		GB-B2- 2015339	15-09-82
		HK-A - 485/85	28-06-85
		IE-B - 48016	05-09-84
		IL-A0- 56790	31-05-79
		IL-A1- 56790	31-01-82
		IT-A0- 7948152	27-02-79
		IT-A - 1115038	03-02-86
		JP-A2-54132223	15-10-79
		JP-B4-62007891	19-02-87
		KE-A - 3516	19-04-85
		MY-A - 134/85	31-12-85
		NL-A - 7901703	11-09-79
		NL-B - 187260	01-03-91
		NL-C - 187260	01-08-91
		NO-A - 790661	10-09-79
		NO-B - 152635	22-07-85
		NO-C - 152635	30-10-85
		NZ-A - 189819	31-05-84
		PH-A - 15159	24-08-82
		PT-A - 69309	01-03-79
		SE-A - 7901683	08-09-79
		SE-B - 445174	09-06-86
		SE-C - 445174	18-09-86
		SG-A - 147/85	16-08-85
		CH-A - 636013	13-05-83
		HU-B - 182920	28-03-84
		ZA-A - 7901056	29-10-80